SEP-13-06 04:50PM FROM-AKERMAN SENTERFITT

5616596313

T-425 P.06

F-719

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.:

10/748,637

Examiner: SCHUBERG, L. J.

Response to June 13, 2006 Office Action

Page-5-

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SEP 1 3 2008

# REMARKS

Claims 1-19 are pending in the application. Claim 4 has been amended to include the full name of the abbreviation "SCI." No new matter has been added by virtue of this amendment and its entry is respectfully requested.

Attached hereto, are the 37 C.F.R. § 1.1.32 Declarations (as "Exhibit A") of the inventors which further explain the differences between the instant invention and the cited references. Consideration and entry is respectfully requested.

#### Claim Objections

Claim 4 is objected to for recitation of SCI. In response Applicants have amended claim 4 to recite the full terminology, i.e. "spinal cord injury." No new matter has been added by virtue of this amendment and its entry is respectfully requested.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant objection.

### Claim Rejections Under 35 U.S.C. § 102

Claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexander et al (US 6,180,355 B1).

Applicants respectfully traverse.

Applicants invention is directed, in part, to method of increasing motility of sperm, by providing from a subject a biological sample comprising sperm and at least one cytokine; and contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF $\alpha$ , 1L1 $\beta$ , and IL6.

(WP333289,1)

T-425 P.07 F-719

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

10/748,637 Application No.: Examiner: SCHUBERG, L. J.

Response to June 13, 2006 Office Action

Page-6-

Alexander et al., neither teaches nor discloses methods of increasing sperm motility. Alexander et al., discusses diagnosing of CPPS. There is no discussion or teaching that administration of anti-cytokine antibodies or agents increase sperm motility. Furthermore, treatment of sexual dysfunction by administering anti-TNFa antibodies with a patient suffering from CPPS has no bearing on treating fertility, i.e. sexual function vs. fertility. Alexander et al., neither teaches nor discloses treatment of actual semen samples with any anti-cytokine agents. In contrast, Alexander et al., discusses systemic administration of an anti-TNF-a antibody.

Applicants further discuss in detail in the 37 C.F.R. Rule 1.132 Declarations (Exhibit "A") filed herewith, that Alexander et al. neither teaches nor discloses the instant invention.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

# Claim Rejections Under 35 U.S.C. § 103

Claims 1-6 and 8-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Basu et al (Journal of Andrology, 2002).

Applicants respectfully traverse.

Alexander has been discussed above. Alexander et al does not teach or disclose the instant invention. Furthermore Alexander discusses sexual dysfunction which is completely different to infertility and sperm mobility. There is no motivation to combine Alexander et al., with Basu et al., as each discuss different conditions and diagnosis of CPPS as discussed by Alexander would not result in a method of treatment infertility as taught by the instant invention. Further, as stated by the inventors in the 37 C.F.R. Rule 1.132 Declaration, Basu is a co-inventor and the conception of the instant application preceded the Basu publication. As such, Basu et al is not a proper reference.

(WP333289.1)

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.:

10/748,637 Examiner: SCHUBERG, L. J.

Response to June 13, 2006 Office Action

Page- 7 -

In view of the foregoing and Applicants Declaration, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 1, 2, 5-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Faber et al. (Obstetrics and Gynecology 2001) and Slesarev (US 5,834,435).

Applicants respectfully traverse.

Applicants have discussed Alexander et al. Faber does not teach or disclose a method of treating sperm mobility using anti-cytokine agents. Faber discusses endometriosis-associated infertility in females. There is no teaching or disclosure in Faber that would motivate one of ordinary skill in the art to treat male infertility nor combine the teachings of Alexander with Faber. Faber does not make up for the deficiencies of Alexander et al. Neither treats male infertility. Slesarev et al., also fails to make up for the deficiencies of Alexander and Faber. Slesarev does not teach or disclose treatment of male infertility. Vaginal application of a compound that inhibits TNFa is irrelevant to treating male infertility.

The Examiner, on page 6, sets out the reasoning for the rejection based on cited references "to treat endometriosis in women..." Applicants submit that treating male infertility as taught by Applicants is not obvious in view of the cited references standing alone or taken together. Further discussion is provided by the declarations of the inventors, filed herewith.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

{WP333289;1}

FROM-AKERMAN SENTERFITT SEP-13-06 04:50PM

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T-425 P.09/40 F-719

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SEP 1 3 2006

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.:

10/748,637 Examiner: SCHUBERG, L. J.

Response to June 13, 2006 Office Action

Page- 8 -

#### CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-19 define patentable subject matter and is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is being timely filed within the shortened statutory period and, as such, Applicants believe that no fees are due. Although, Applicants believe that no extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any further extensions of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

> Respectfully submitted, **AKERMAN SENTERFITT**

Date: September 13, 2006

Nicholas A. Zachariades, Ph.D.

Reg. No. 56,712

AKERMAN SENTERFITT

P.O. Box 3188

West Palm Beach, FL 33402-3188

Tel: 561-653-5000

Docket No. 7230-9

**CENTRAL FAX CENTER BECEINED** 

**SEP 13 2868** 

Pop. No. 64,712 COMPREAMS UNDER 37 CFR 1.850 封ま

Syaminar: SCHUBGRO, L. J.

Group: 1651

December 10, 2003

10/748,637

Confirmation No: 6890

In co Application of: Brackett N. L., et al.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

7

EXHIBIT 'A'

TCER LIMBELARATION

Commissioner for Patents Mail Sup Amendment

I, Noney L. Brackett, declare as follows:

107748,637 exitted "INCREASING SPERIM MOTLITY" (hereafter the '637 application) and I am one of the numed inventors and am familiar with patent application No. On rubject matter described therein.

presently employed as a Research Associate Professor of Neurological Stuggery and Urabogy, I hold a Pt.D. in Behavioral Neuroscience and an UCLD in Andrelogy. I am University of Asiani Miller School of Medicine. I have worked in the field of reproductive ہے

BEST AVAILABLE COPY

Sep. 12.

2006 12:35PM

Via Facedmillo No. 571 -371-8100

Alexandria, VA 22313-1450 P.O. Box 1450

(UPSSELDE41)

RULB 122 DBCLARATION
In 12 Application of: Brackett N. L., et al.
Construction No. 6890
Application No.: 10748,617
Prest - 2 -

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biology for 10 years. My expectise is in Andrology and male infertility, specifically infertility of men with spinal cord lejesy.

- Chave authored or combored more than 50 scientific papers.
- I have reviewed the Office Action datal June 13, 2006 and references ailed

therein. I have been arked by patest counsel Zacharlades to provide an explanation based on the claimed invention showing that the subject moder of the claims differs from the cited ant.

independent claim I is copied below.

Chin I. A method of inarousing mobility of merm, the method comprising the

steps of:

n) providing from a subject a biological sampte comprising sperm and at least one

cytoking and

6) contracting the biological mapte with an agent that inactivates or reduces the blotogical activity of the at feast one cytokine extected from the group consisting of TNFG, ILIB.

and ILA

5. The Exeminar has rejected dalms 1, 2, 5, 8.19 are rejected under 33 U.S.C. §102(b) as being anticipated by Alexander et al. (US 6,180,355 B1). The Examinar has also rejected chains 1-6 and 8-10 under 15 U.S.C. §103(a) as being unpartentiable over Alexander et al. (US 6,180,355 B1) in view of Bass et al. (Journal of Anthrology 1002), Claims 1, 2, and 5-

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(1 PATOLINA)

Sep. 12. 2006 12:35PM

No. 0420

RULB 112 DECLARATION In re Application of Brackett N. L., et al. Confirmation No: 6890 Application No: 107148,637

ÿ 812-3 19 were rejected under 15 U.S.C. §107(s) sa being imprisonable over Alexandor es et (US 6,180,355 BI) in view of Petrox et el. (Obstepries and Cynecology 2001) and Sleenery (US

5,834,435).

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No. 0420

P.12/40

First, I will discuss the Alexander et al. (US 6,180,755 Bl) reference and why this patent does not bach or disclose the metant invention. ø

remined platms can be used as "Indicators or confirmatory indecators" of CPPS or an associated Alexandar interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patens. durnic pelvic pain syndroma (CPPS). Sumply pal, Alexander discusses that oylokines in the disorder. Alexander delines CPPS as the pressure of leukocytools in the expressed prostatic The Alexander percent discusses the use of cytokiness as indicators to Irolp diagnoses secretions or by sodiment found in a unine sample exercted following a prortato massage. Alexender discusses the condition(s) with respect to sexual function. Alexander discusses a "trustned of treating a condition associated with elevated levels of a offective amount of an east-cytolone..." Parther, all treatments (aught in the Alexander patent are cytoldine, such as TNP-alpha, in seminal plessna, accaprising administering a therapecatically by systemic administration of oral or parcoterni agents.

The lastant invention is not laught or dischosed by Alexander et al.

Sep. 12. 5006 12:35PM

[HASTI EBAN]

RULB (12 DECLARATION fn to Application of: Bracket N. L., et ul. Confirmation No: 6890 Application No: 101748,637 Pago - 6 — The Examines wroughy interprets Alexander's tooching, i.e., the Examines that effects on rexust fraction she occur to fertility. The Braniner's sexumption is not supported by may fibels or examples in the Alexander patent, nor is this assumption connect in the medical field.

Our potent addresses tow sperm mobility, not a condition of sexual dysfunction.

As described, Alexander uses cytetians so "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patent does not use cytetians to diagnors a discuss. Indead, our patent states that cytetians are agains in the semen which act immediately on sparm cells to reduce their multity in the ejecutate. Prior to contact with the semen cytefines, sperm cells to reduce their motifity in the ejecutate. Prior to contact with the semen cytefines, sperm cells to require normal or near normal.

Alexander discusses a "wethod of treasing a condition associated with clevels of a cytokine, such as TNP-alphe, in sentiral plasma, comprising administering a therapenitially effective amount of an arti-artotine...\* The "condition" clearly referred to in the Alexander patent is CPPS or a similar consistent, and the presence of this cytokines themselves, as is the case in our patent. Our target group is not men with CPPS, but ones with spinal cord injury. Our patent does not claim that CPPS causes decreased sperm analisty.

All enstruents trught in the Alexander patent are by systemic adoublismation of orst or parestend agents. In the Alexander patent, there is no provision for treating the senson. In the

(WPL)QZB4:1)

Sep. 12. 2006 12:35PM

RULG 172 DECLARATION for a Application of Dracket N. L., et al. Confirmation No. 6850 Application No.: 10748,637

9

patent provides for treating the somes to improve the coadition of low spers motility in wen medical field, there is no basis for assuming that bearing the somen will improve CPPS. Our with spinal cord tojury. Second, I will discuss the Basu of of, reference and why this relatione does not teach or disclose the Instant in vertion. ÷

stactorum was submitted to the University of Milani on huly 11, 2002. The date of conception as layenters. (1 is my understanding that the invention disclosure date is the key date. The invention listed on the invention Direlosues form was lan. 12, 2001. The examinee asserts that "one of Alexander discusses that the method can be used to trest conditions associated with elevated Some of the Etuminat's objections are based on publications by Bears. The Examina ardinary skill in the act would have been mativated to use the method of Alexandes because betieves that these Barn publications proceeded the potent application. Basn is one of our colevels of a sytaline ....."

nonstina, low sporm motility, by the addition anti cytokina agents to the seminal plasma in vitro ades instruction of eath cytotions against oreally or parentically. Our method treats an surrelated Once again, we assert that the method referred to treats conditions such as CPPS by (see above).

[WPXXXX64;]

250 12 2006 12:36PM

No. 0420

No. 0420 L .9

RULB 131 DECLARATION [nee Application of: Brackett N. c. al. Confirmation No: 6890 Application No: 10748,637 Pags - 6 –

sperm to the exact pollucide. It discusses infartifity is women coused or related to andometriosis. cytokines in the peciformal fluid of women with endometrionis and their effect on the binding of Third, I will discuss the Fabor of al. reference and why this reference does not teach or disclose the instant (nyentlan. The reference discusses the recentrates of certain œ

The instant invention is not taught or disclosed by Paber et al.

som blading. There is no suggestion on their part or reasonatelo modical conclusion that can be resched that teaches that treating spein in the ejeculate will or may retreaty this affliction of the Poter does not aussure or evaluate spern motility. Umenures the interaction of sperm with a contain parties of the arvorn and notes that aromen with endometricals may have clavated level of cytokines in Cheir peritonesi Muld and falopian tubas that may interfere with sparm -Amale reproductive tract.

PAGE 15/40 \* RCVD AT 9/13/2005 4:51:06 PM [Eastern Daylight Time] \* SVR:USPTO-EFXRF-615 \* DNIS:2738300 \* CSID:5016995313 \* DURATION (mm-5s):05-06

The examiner states that perionnel Maid is produced from the reproductive trats. This is factually incorrect Fourth, I will disputs the Stesmov reference and why this reference does not teach lpha discipas the instant toversion. The reference discusses the system is effects of TNF-stepta in a watery of toxic and other that conditions as well as yre term labor and the role of a octain muramyl dipoptide (QNDP) in modulating these effects, specifically the synthesis of ď

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RULE 132 DOCLARATION for a Application of Boackett N. L., ct al. Confirmation No: 6890 Application No: 10/748,537

8

611-7

prostaglanda E2. This probiotic maranay peptide is a component of the booterial celf wall of cormal vegloal flors and may also be found in human amplotic fluid.

The Instant Invention is not taught or disclosed by Stesarev et al:

uchievo systemia shsoopitaa. Ia this ucting, we do not agree that "one of ordinary skill in the art method] because Steamov had proviously administered vagnarity a compound that teletios TNPsloper. Again, we propose treating a local condition, low sperm modity, rather than a systemic and of "programmy toxicity". In another instanca, the vaginal application secure to be included mantitoted or reggested in the discussion of the effects of TNF-alpia or the modulation of its effects. Slessrey proposed the veginal application of OMPD as streatment of proteon (abor with all other methods of edministration, (oral, topical, rectst, and as a food supplement) to would have had a recessable expectation of mockes [in treating low sperm modility by our Neither male instatility nor low appear motility or my other sperm abmormality is condition.

I further easte that all statements made herein are of my own knowledge are two and that all statements made on information and bolisf are believed to be true; and further that made are punishable by line or impolecement, or both, under § 1001 of Title 18 of the Valted bece structurents were made with my knowledge that willful false statements and the like so 9

266-12, 2006 12:36PM

P.16/40 1-425 2818288313

No. 0420

(MP3DZZZEN)

RULE 132 DECLARATION fr so Application of: Brackett N. L., et al. Confirmation No. 6890 Application No.: 10718,637 Page · 8 -

Butes Code, and that ruch willful falce statements may joopardize the validity of the application

or any patent issued themon.

(MP33335451)

8ep. 12. 2006 12:36PM

SEP 1 3 2006

#### EXHIBIT "A"

#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.:

10/748,637

Examiner: SCHUBERG, L. J.

Date Filed:

December 30, 2003

Group: 1651

For: INCREASING SPERM MOTILITY

CERTIFICATE UNDER 37 CFR 1.8(a) I hereby certify that this correspondence is being deposited either by facstrille to 571-273-8300 or with the U.S. Postal Service as First Class mail in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on 2006

Nicholas A. Zachariadas

Non \_, Reg. No. 56,712

#### 37 C.F.R. 1.132 DECLARATION

Via Facsimile No. 571-273-8300

Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

#### I, Sarmistha Basu, declare as follows:

- I am one of the named inventors and am familiar with patent application No. 1. 10/748,637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.
- I hold a Ph.D. in Science (Biochemistry). I am presently employed as Program Manager at Dow Pharmaceutical Sciences, Inc., Petaluma, California for last 5 years. I have worked in the field of Biochemistry for 7 years.
  - I have authored or coauthored more than 6 scientific papers.

(WP333251;1)

RULE 132 DECLARATION
In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637

Page - 2 -

4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by parent counsel Zachanades to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art. Independent claim 1 is copied below.

- Claim 1. A method of increasing motility of sperm, the method comprising the steps of:
- a) providing from a subject a biological sample comprising sperm and at least one cytokine; and
- b) contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNFα, IL1β, and IL6.
- 5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander et al. (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Basu et al. (Journal of Andrology 2002). Claims 1, 2, and 5-19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Faber et al. (Obstetrics and Gynecology 2001) and Slesarev (US 5,834,435).

(WP333251:1)

**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 3 -

First, I will discuss the Alexander et al (US 6,180,355 B1) reference and why this 6.

patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose

chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the

seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated

disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic

secretions or by sediment found in a urine sample excreted following a prostate massage.

Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent.

Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a

cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically

effective amount of an anti-cytokine..." Further, all treatments raught in the Alexander patent are

by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander et al.

The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that

effects on sexual function also occur to fertility. The Examiner's assumption is not supported by

any facts or examples in the Alexander patent, nor is this assumption correct in the medical field.

Our patent addresses low sperm motility, not a condition of sexual dysfunction.

(WP333251:1)

PAGE 20/40 \* RCVD AT 9/13/2006 4:51:06 PM [Eastern Daylight Time] \* SVR:USPTO-EFXRF-5/5 \* DNIS:2738300 \* CSID:5616596313 \* DURATION (mm-ss):05-06

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**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 4 -

As described, Alexander uses cytokines as "indicators or confirmatory indicators" of

CPPS. In contrast to the Alexander patent, our patent does not use cytokines to diagnose a

disease. Instead, our patent states that cytokines are agents in the semen which act immediately

on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines,

sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a

cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically

effective amount of an anti-cytokine..." The "condition" clearly referred to in the Alexander

patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case

in our patent. Our target group is not men with CPPS, but men with spinal cord injury. Our

patent does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by systemic administration of oral or

parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the

medical field, there is no basis for assuming that treating the semen will improve CPPS. Our

patent provides for treating the semen to improve the condition of low sperm motility in men

with spinal cord injury.

(WP333251;1)

PAGE 21/40 \* RCVD AT 9/13/2006 4:51:06 PM [Eastern Daylight Time] \* SVR:USPTO-EFXRF-5/5 \* DHIS:2738300 \* CSID:5616596313 \* DURATION (mm-ss):05-06

**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 5 -

Second, I will discuss the Basu et al. reference and why this reference does not 7. teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the patent application. Basu is one of our coinventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was lan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discusses that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma in vitro (see above).

Third, I will discuss the Faber et al. reference and why this reference does not 8. teach or disclose the instant invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pellucida. It discusses infertility in women caused or related to endometriosis.

The instant invention is not taught or disclosed by Faber et al.

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated

{WP333251;1}

**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 6 -

levels of cytokines in their peritoneal fluid and fallopian tubes that may interfere with sperm — zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that treating sperm in the ejaculate will or may remedy this affliction of the female reproductive tract.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the Slesarev reference and why this reference does not teach or disclose the instant invention. The reference discusses the systemic effects of TNF-alpha in a variety of toxic and often fatal conditions as well as pre term labor and the role of a certain muramyl dipeptide (GMDP) in modulating these effects, specifically the synthesis of prostaglandin 62. This probiotic muramyl peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev et al:

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of GMPD as a treatment of pre-term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-

{WP333261;1}

T-425 P.24/40 F-719

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SEP 1 3 2006

**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 7 -

alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

I further state that all statements made herein are of my own knowledge are true 10. and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

servistra Basre

09/13/06

EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No: 6830 In to Application of Brushell N. L., et al.

Application No.: 10748 617

Examiner: SCHUBBRG, L. J.

Pos: INCREASING SPURM MOTILITY Date Filed:

Occup; 1651

December 30, 2003

17 C.P.R. L. 132 DECTARATION

Via Pacsimide No. 571-277-8100

Alexandria, VA 22313-1450 Mail Stop Amendment Commissioner for Putcuds P.O. Box 1450

[, Charles M. Lymo, doctare as follows:

(, ) Less one of the cerned inventors and was families with potent application. No.

197748,637 caulded "INCREASINO SPERM MOTULITY" (kaccafter the '637 application) and

the subject matter described therein.

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(WP22928QL !)

Sep. 12. 2006 M964:1

RULB 132 DECLARATION la ra Applicacion of: Brackett N. L., et al. Cantimentan No: 6830 Applicacion No: 10748,637 Prese - 2 –

ξ ٩.

811-4

I hold an MD and new board condited in Urology. I am presently amployed as a Professor of Urology at the University of Miller School of Medicine. I ture worked in the field of Undagy for 95 years.

No. 0421

T-425

P.26/40

- I have authored or convilioned more than 70 scientific papers.
- I have reviewed the Office Action dated Inv 13, 2006 and references vited

therein. I have been seked by patent counsel Zachidiades to provide an explanation based on the claimed invention showing that the subject motter of the claims differs from the cited ort.

Independent claim list capied below.

A method of Increasing maility of them, the method comprising the Carre

steps of:

a) providing from a subject a biological sample compissing sperm and at least one

cytokine, and

b) contecting the blokapical eample with an agent that insertivates or reduces the

biological petivity of the at least one cytak inc artected from the group consisting of INPA, ILIP,

and 11.6.

al (US 6,180,355 BI) in view of Basu et al. (fourted of Andrology 2002). Claims 1, 2, and 5rejected claims 1 4 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexandas at The Braminer has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being naticips ted by Alexander et al. (US 6,180,355 B1). The Examiner fixed also ٨;

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RULE 17 DECLATATION lo re Application of Brakert N. L., et al. Confirmation No. 6890 Application No.: 1074&637 19 were rejected under 35 U.S.C. § 101(a) as being ungatantable over Alexander et al. (US 6,180,355 B1) in view of Police et al. (Obsecutive and Cyrocology 2001) and Sleaney (US

5,834,435).

6. First, [ will dissues the Abrander et al. (US 6,180,355 B() sulceence and why this

patent does not teach or disclose the lastnat lawnslan

The Alexander patent discusses the use of cytokines as indicators to thelp disgnost choose special syndrome (CFPS). Simply put, Alexander discusses that cytolines in the standard polyte pain syndrome (CFPS). Simply put, Alexander discusses that cytolines in the standard to be used as "indicators are an illuminary indicatory" of CPPS or an associated standarder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic corrections or by sediment found in a urine sample exceeded following a prostate massage.

Alexander interthanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Abgender discusses a "melhod of treating a corntition associated with elevated levels of a cytokine, such as TAP-alpha, in seminal plasma, comprising administering a therapentically effective amount of an anti-cytokine..." Forther, all treatments tanght in the Abensader patent are by systemic administration of oral or parenteen agends.

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RUKE 132 DECLARATION fn re Application of: Brackell N. L., et al. Conlinnation No: 6890 Application No: 107749 £37 Page - 4 –

any shets or examples in the Abecamber patent, oor is this uscumption correct in the medical sfeld. effects on reusal function also occur to fertility. The Examiner's assumption is not supported by The Examinar woughly interprots Alexander's teaching, i.e., the Braminar assumes that Our painet addresses fow sperm moditivy, not a coadition of sexual dysfunction.

on sperm cells to reduce their motility in the ejeculate. Prior to consist with the serven optoblides, discass, instead, our paient states that cytokines are agents in the senten which act immediately As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander polent, our polent then not use cytoldnes in Anggrass o apen motility is normal or aree normal. Alcaender discusses a "mathod of treating a condition associated with elevated levels of a potent is CPPS or a similar condition, not the presence of the cytokioses themselves, as is the case efective sasant of an anti-cylokins..." The "condition" clearly referred to in the Alexander cytoluina, ench as TNF-alpha, ia seminal pharm, comprising odministratug a therspeculically is our patent. Our larged group is not men with CPPS, but men with spinal cond injury. Our patent does not claim that CFPS causes decreased sporm mobility.

All treatments bught in the Alexandee potent are by systemic extensionation of onal or parenteral agenta, in the Alexander patent, there is no provision for trensing the semen. In the

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RUBB 132 DECLARATION In the Application of Backett N. L. et al. Confirmation No: 6390 Application No: (0748 £17

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patent provides for breating the sensen to improve the condition of low spars motifity in men medical field, there is no basis for assuming that treating the senion will improve CPPS. Our with spinol cord injury. Second, I will discuss the Basa of al. reference and way this reference does not teses or disclose the instart invention. ۲.

electorare was submitted to the University of Mismi on July 11, 2002. The data of conception as treators. It is my understanding that the invention disclosure date in the key then The forestion listed on the favoration Disclasure form was Ino. 12, 2001. The communic asserts that "one of Alexander discusses that the method can be used to treat conditions associated with elevated Some of the Exeminar's objections are besed on publications by Basi. The Examina ordinary skill in the art would have been motivated to use the method of Alexander because believes that these Barn publications proceded the patent application. Barn is one of our colevels of a cytokino......"

condition, fore sperm mot lity, by the addition not sytakins agants to the seminal plasms in vitro ulamistration of eati cytokios agents anily or parestacisty. Our method treats an unrelated Once again, we assert that the malbod referred to treate conditions such as CPPS by (see above).

Sep. 12. 2006

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FROM-AKERWAN SENTERFITT

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No. 0421

RULE 132 DECLARATION In re Application of: Bracket N. L., et al. Confirmation No: 6890 Application No:: 10748 £17 Page - 6 –

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8. Third, I will discuss the Fabor et al. reference and why fils reference does and track or discloss the instant invention. The reference discusses the occurrence of octabn cytokines in the performed fluid of women with endometriesis and their effect on the binding of sperm to the zone pelluids. It discusses infertility in women exused or related to endometriesis:

The Instant invention is not taught or disclosed by Paber et al.

Faces does not measure or evaluate sperm motifity. It measures the interaction of sperm with a cartain portion of like ovum and notes that women with endometricais may lave clouded toward covals of cytokines in their peritoneal fluid and fallopina takes that may interfere with spenn – man binding. There is no suggestion on their part or reasonable modical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the famile reproductive tract.

The casminer stakes that particules fluid is produced from the reproductive tract. This is security incorrect. 9. Frouth, I will discuss the Slessurer reference and why this reference does not teach or disclose the instant invention. The reference discusses the system is officets of TNR-alpha in a variety of toxic and office fatal conditions as well as pre-term taker and the role of a contain awarency dipeptide (GMEP) in modulating these effects, specifically the sysubcess of

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prostagandia Et. This problotic muranny) peptide is a component of the bacterial cell wall of oormal vaginal flora and may also be found in burnen arraiotic fluid.

The instant invention is not taught or disclosed by Slessner et ak

netherne systemic obsurption. In this acting, we do ted sgree that "one of ordinary skill in the ast alpha". Again, we propered treating a local condition, low sperm modility, rether than a syntemic metinal because Stearev had proviously administrated vaginally a compound that inhibits TNPend of "pregnancy toxicity". In another instance, the engined application seems to be included mentioned or suggested in the discussion of the effects of TNF-sights or the modulation of its effects. Securiv proposed the vaginal application of CAAPO as a treatment of pro term labor with all other methods of administration, (ord, topical, roctal, and us a food supplement) to would have bad a reasonable expectation of success in breaking low sperm mothisty by our Neither note in feetlify nor low sperm motility or any other sperm about maility is coodition.

( further state that ut) statements made herein are of my own knowledge are true and tast all statements made on information and betief are bolieved to be true, and further that made are praistable by line of imptisonment, or both, under §1001 of Tide 18 of the United these statements were matte with my knowledge that willful false statements and the like so ರ್ಷ

Sep. 12. 2006

M964:1

No. 0421

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PAGE 32/40 \* RCVD AT 9/13/2006 4:51:06 PM [Eastern Daylight Time] \* SVR:USPTO-EFXRF-515 \* DNIS:2738300 \* CSID:5616596313 \* DURATION (mm-55):05-06

RULE 112 DECLAIMITON In re Application of: Urackett N. L., et el. Confirmation No: 6890 Application No: 107148,637 Pogn - 8 –

or any patent issued thereon.

Or. Charles M. Lynne

(HPCCCCS6011)

Sep. 12. 2006 1:50PM

No. 0421 T-425 P.32/40 F-719

Sintes Code, and that such willful false statements may jeopardize the validity of the application

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FROM-AKERMAN SENTERFITT ZEb-13-08 04:23bM

T-425 P.33/40 F-719

# EXHIBIT "A"

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brackett N. L., et al.

9143527517

Confirmation No: 6890

Application No.:

10/748,637

Examiner: SCHUBERG, L. J.

Date Filed:

09/11/2006 10:50

December 30, 2003

Group: 1651

For: INCREASING SPERM MOTILITY

CERTIFICATE UNDER S7 CFR 1.8(a)
I haraby certify that this correspondence is being deposited either by facilities to 571-273-8300 or with the U.S. Postal Service as First Clear mall in an envelope addresses to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on 64-13 2008

\_, Reg. No. 56,712

Nicholas A. Zacharisdas

# 37 C.F.R. 1.132 DECLARATION

Via Facsimile No. 571-273-8300

Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

#### I. Daniel R. Cohen, declare as follows:

- 1. I am one of the named inventors and am familiar with patent application No. 10/748,637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.
- 2. I hold a Medical Doctor degree in Gynecology and a Medical Doctor degree in Medical Genetics. I am presently employed as Medical Director at Second Medical Opinion Services-Gracias Doctor Corporation & American Health National Network-. I have worked in (WP339253;1)

09/11/2006 10:50

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RULE 132 DECLARATION
In re Application of: Brackett N. L., et al.
Confirmation No.: 6890
Application No.: 10/748,637
Page - 2 -

the field of prenatal diagnosis of genetic diseases, cytogenetics and molecular biology (Northern Blot, Southern Blot, mitochondrial DNA sequencing, and microarray DNA technology

- I have authored or coamhored more than 11 scientific papers, and one patent.
   in Argentina (Continue cloning keratinocytes stem cell system for skin culture)
- 4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by patent counsel Zachariades to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art. Independent claim 1 is copied below.
- Claim 1. A method of increasing morility of sparm, the method comprising the steps of:
- a) providing from a subject a biological sample comprising sparm and at least one cytokine; and
- b) contacting the biological sample with an agent that inactivates or reduces the
   biological activity of the at least one cytokine selected from the group consisting of TNFα, IL1β,
   and IL6.
- 5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander et al. (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Basu et al. (Journal of Andrology 2002). Claims 1, 2, and 5-(WP333253:1)

**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

9143527517

Confirmation No: 6890 Application No.: 10/748,637

Page - 3 -

09/11/2005 18:50

19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Faber et al. (Obstetrics and Gynecology 2001) and Slesarev (US 5,834,435).

6. First, I will discuss the Alexander et al. (US 6,180,355 B1) reference and why this patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic secretions or by sediment found in a urine sample excreted following a prostate massage.

Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander et al.

(WP933253:1)

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PAGE 84

**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 4 -

09/11/2005 10:50

The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that effects on sexual function also occur to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patent addresses low sperm motility, not a condition of sexual dysfunction.

As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patent does not use cytokines to diagnose a disease. Instead, our patent states that cytokines are agents in the semen which act immediately on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." The "condition" clearly referred to in the Alexander patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case in our patent. Our target group is not men with CPPS, but men with spinal cord injury. Our patent does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the

(WP933253;1)

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PAGE 05

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.

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Confirmation No: 6890 Application No: 10/748,637

Page - 5 -

89/11/2086 10:58

medical field, there is no hasis for assuming that treating the semen will improve CPPS. Our patent provides for treating the semen to improve the condition of low sperm motility in men with spinal cord injury.

7. Second, I will discuss the Basu et al. reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the parent application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discusses that the method can be used to treat conditions associated with elevated levels of a cytokine......"

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti-cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti-cytokine agents to the seminal plasma in vitro (see above).

(WP333253;1)

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**RULE 132 DECLARATION** 

In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 6 -

8. Third, I will discuss the Faber et al. reference and why this reference does not teach or disclose the instant invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pellucida. It discusses infertility in women caused or related to endometriosis.

The instant invention is not taught or disclosed by Faber et al.

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated levels of cytokines in their peritoneal fluid and fallopian tubes that may interfere with sperm—zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the female reproductive tract.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the Slesarev reference and why this reference does not teach or disclose the instant invention. The reference discusses the systemic effects of TNP-alpha in a variety of toxic and often fatal conditions as well as pre term labor and the role of a certain muramyl dipeptide (GMDP) in modulating these effects, specifically the synthesis of

(wp333253;1)

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**RULE 132 DECLARATION** In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 7 -

prostaglandin E2. This probiotic muramyl peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev et al:

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of GMPD as a treatment of pre term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNFalpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

I further state that all statements made herein are of my own knowledge are true 10. and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United

(WP333253;1)

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PAGE 88

RULE 132 DECLARATION In re Application of: Brackett N. L., et al.

Confirmation No: 6890 Application No.: 10/748,637

Page - 8 -

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States Code, and that such willful false statements may jeopardize the validity of the application

or any patent issued thereon.

9-12-2006

(WP3332E3;1)